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Secondary amyloidosis due to Schistosoma mansoni infection

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Summary

Four children with Schistosoma mansoni infection and the nephrotic syndrome with varying degrees of renal dysfunction were found on histological examination to have amyloidosis. In one boy who had no evidence of renal failure complete clinical regression of his nephrotic syndrome and almost complete disappearance of renal amyloid deposits followed adequate treatment of his schistosomal infection. Conditions known to cause secondary amyloidosis were excluded in all four patients. Amyloidosis in association with mansoni infection is probably more common than is currently recognised. Early treatment of the infection, before renal function becomes impaired, may result in regression of the amyloidosis.

Introduction

The skewing of the age incidence of nephrosis in Nigeria with a peak at 8 years lead to the suggestion[1] that quartan malaria may be a primary cause. This suggestion was later proved by immunopathological studies[2] that showed deposits of IgM and C3 complexes in glomerular capillary walls. This relation between quartan malaria and nephrosis has led to the suggestion[3] that similar associations may exist between nephrosis and other infections, especially schistosomiasis. In areas where schistosomiasis is common and where the age incidence of nephrosis is similar to that identified in Nigeria comparable mechanisms relating schistosomiasis to nephrosis would be expected. Work from South America[4 5] has shown a uniform pattern of kidney lesions in patients with hepatosplenic schistosomiasis. In these studies focal electron-dense deposits were seen that corresponded to γ-globulin and complement as shown by immunofluorescence microscopy, but no cases of amyloidosis were described. We have recently examined seven children with schistosomiasis and renal disease.

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Patients and methods

In the first patient with schistosomiasis and nephrosis amyloidosis was suspected on clinical grounds, so a specific stain for amyloid was used on biopsy material. Six more children with *Schistosoma mansoni* infection and the nephrotic syndrome or renal dysfunction, or both, were subsequently seen. Two died soon after admission and permission for necropsy was refused, and in one patient it was impossible to perform a renal biopsy. The remaining three children and the first patient are the subject of this report.

In all four chest *x*-ray and skeletal surveys showed nothing abnormal. Lupus erythematosus cell preparation, rheumatoid factor, and Kahn and Wasserman reaction test results were negative. Haemoglobin electrophoresis showed Hb AA in all four patients. Cerebrospinal fluid was normal and there was no clinical indication of leprosy. In all patients the diagnosis of amyloid was based on Congo-red staining and birefringence to polarised light.

Case 1

A 10-year-old boy was admitted on 10 May 1974 with a five-month history of progressive ascites and generalised oedema. Examination showed gross anasarca, blood pressure of 120/80 mm Hg, and hepatomegaly to 7 cm below the right costal margin, with prominent enlargement of the left lobe with a smooth and firm surface. The spleen was palpable 6 cm below the left costal margin. Haemoglobin was 9·5 g/dl, packed cell volume 31%, total plasma proteins 53 g/l, albumin 27 g/l, serum cholesterol 7·5 mmol/l (290 mg/100 ml), blood urea 5·2 mmol/l (31 mg/100 ml), and 24-hour urinary protein excretion 6·3 g. Stool examination showed no parasites. Treatment with a high protein diet and diuretics was started. Liver biopsy on 6 June 1974 showed several schistosomal granulomata and extensive amyloid deposits. Subsequently proctoscopy and examination of a rectal snip showed viable schistosoma ova. Percutaneous renal biopsy showed extensive amyloid deposits (figs 1 and 2) in all glomeruli and in tubular basement membrane and artery walls. His schistosomiasis was treated with a single injection of hycanthone (Etrenol).

After three months 24-hour urinary protein fell to 0·15 g. There was no oedema, the liver was just palpable on deep inspiration, and the spleen could not be palpated. Haemoglobin was 10·1 g/dl, total plasma protein 72 g/l, albumin 40 g/l, serum cholesterol 5·1 mmol/l (195 mg/100 ml), and blood urea 4·0 mmol/l (24 mg/100 ml). Liver biopsy showed that amyloid deposits had almost completely disappeared, and renal deposits had regressed considerably. Six months after

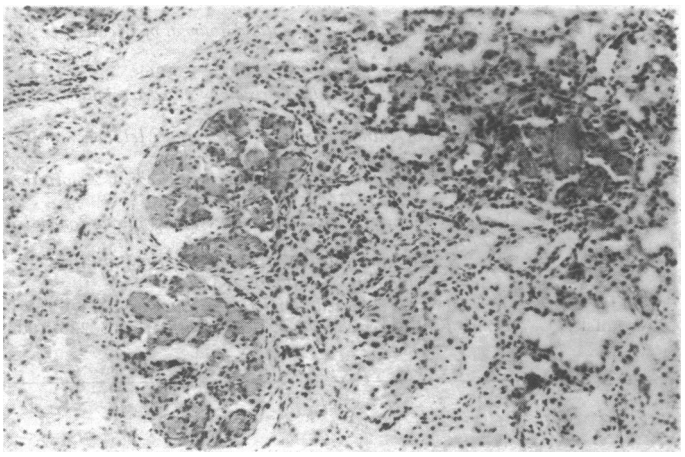

FIG 1—Case 1. Renal biopsy specimen showing extensive amyloid deposits in glomeruli. (Congo red × 62.)

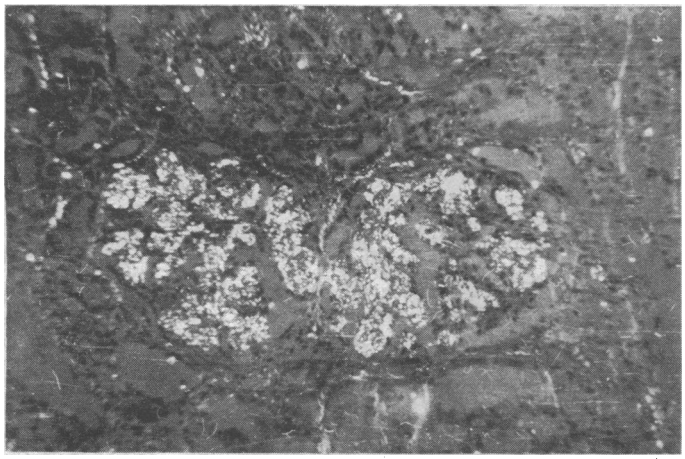

FIG 2—Case 1. Renal biopsy showing amyloid deposits in glomeruli that gave strong coarse positive birefringence under polarised light. (Congo red, polarised light × 102.)

treatment there was no abnormality on clinical examination and the third renal biopsy showed all glomeruli almost completely free of amyloid deposits. In contrast to the initial biopsy findings the tubular basement membrane and arteries did not contain amyloid.

Case 2

A 12-year-old schoolboy was admitted to hospital on 15 April 1974 because of fever, vomiting, and grand-mal seizures one day before admission. On examination he was drowsy with a temperature of 40°C. His liver was enlarged to 8 cm below the right costal margin and the spleen was at the umbilical level. An immediate blood film showed malignant tertian malaria parasites. He was treated with intravenous fluids, chloroquine phosphate, and paraldehyde and was reasonably well on the third day after admission. Subsequent investigations showed viable *S mansoni* ova in the stools; urine showed moderate proteinuria. His blood urea was 32·7 (197 mg/100 ml), and it ranged from 15·6 to 22·2 mmol/l (94 to 134 mg/100 ml) while he was on a low-protein high-carbohydrate diet during his stay in hospital. Total plasma protein was 77 g/l, albumin 40 g/l, and 24-hour urinary protein 1·8 g. He was treated with Niridazole (Ambilhar) for his schistosomiasis and discharged on 25 May in good condition. Seven months later he complained of tiredness and a poor appetite. Liver and spleen were still at the same level as before, and repeated stool examination and rectal snips did not show schistosoma ova. Blood urea was 18·9 mmol/l (114 mg/100 ml), haemoglobin 7 g/dl, 24-hour urinary protein 1·3 g, and creatinine clearance was 16 ml/min. Heavy amyloid deposits were seen in both liver and kidney (fig 3) biopsy specimens. His renal function remained the same five months later.

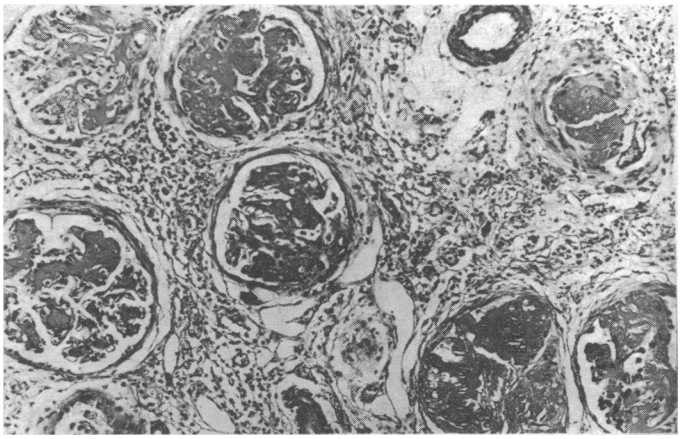

FIG 3—Case 2. Renal biopsy showing extensive amyloid deposits in glomeruli and arteries. (Congo red × 56.)

Case 3

A 13-year-old boy was admitted on 20 January 1975 because of a two-month history of progressive generalised oedema. Examination showed pallor, gross anasarca, and a blood pressure of 150/100 mm Hg. The liver was palpable 7 cm below the right costal margin, and the spleen was palpable 5 cm below the left costal margin. Stool examination showed viable *S mansoni* ova. Investigations showed: haemoglobin 8·2 g/dl; packed cell volume 26%; erythrocyte sedimentation rate 123 mm in one hour (Westergren); white blood count 4·6 × 10^9/l (4600/mm^3) with 12% eosinophils; urinary protein excretion 5·4 g; blood urea 68·1 mmol/l (410 mg/100 ml); serum sodium 147 mmol/l (147 mEq/l); serum potassium 4·3 mmol/l (4·3 mEq/l); total plasma protein 65 g/l, albumin 29 g/l; serum calcium 2·0 mmol/l (8·1 mg/100 ml); serum phosphorus 4·1 mmol/l (12·8 mg/100 ml); and serum cholesterol 8·0 mmol/l (310 mg/100 ml). He was treated with a single injection of hycanthone and diuretics, which produced some improvement in his oedema, but he subsequently developed melaena and his renal function deteriorated progressively and he died on 6 April 1975.

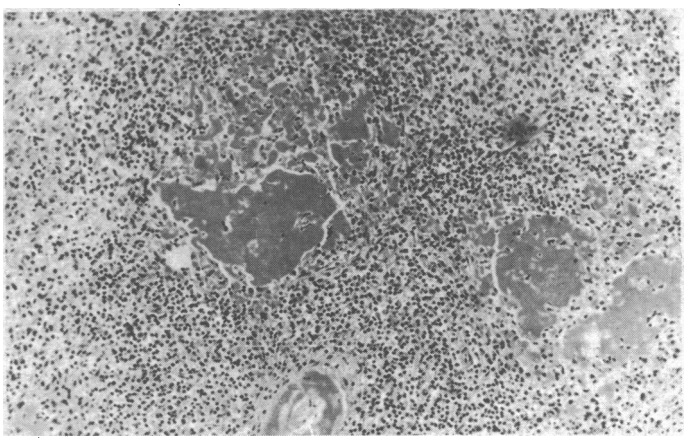

FIG 4—Case 3. Section of spleen showing amyloid deposits in malpighian corpuscles and arteries. (Congo red × 56.)

The essential necropsy findings were the absence of other diseases that could have caused amyloid. Histologically the picture was that of generalised amyloidosis with the heaviest deposits in the kidney and spleen (fig 4) and to a lesser extent in liver, lungs, heart (fig 5), pancreas, adrenals, and large intestine. *S mansoni* ova or worms, or both, with or without granulomata were found in the large intestine, liver, lung, and pancreas.

Case 4

This 12-year-old boy presented on 2 April 1975 with oedema and ascites that had appeared one month before admission and had

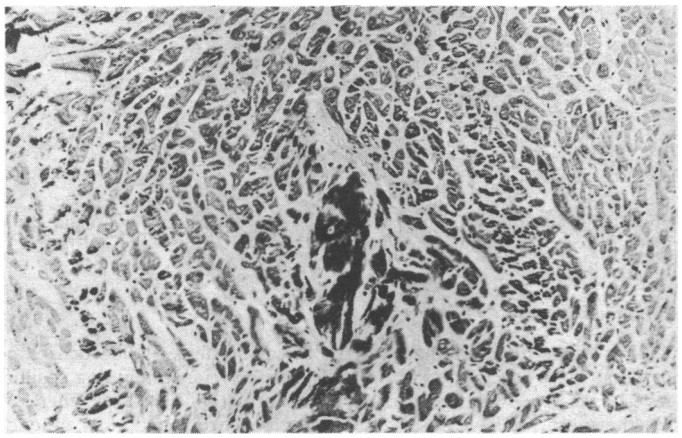

FIG 5—Case 3. Section of heart showing amyloid deposits in myocardium. (Congo red × 56.)

gradually got worse. The liver and spleen were both enlarged to 5 cm below the costal margins. Blood pressure was 110/75 mm Hg. His 24-hour urinary protein excretion was 10·2 g, total plasma protein 42 g/l, albumin 19 g/l, and blood urea 11·0 mmol/l (66 mg/100 ml). Electrolytes were normal. Liver biopsy showed amyloid deposits. Percutaneous renal biopsy showed deposits of amyloid in all the glomeruli (fig 6). He was treated with hycanthone.

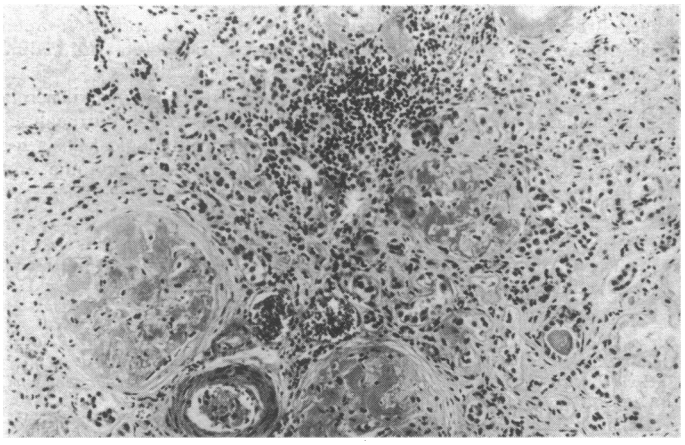

FIG 6—Case 4. Renal biopsy showing amyloid deposits in glomeruli and arteries. Upper right part shows focus of lymphocytic infiltration. (Congo red × 56.)

Discussion

These four cases present evidence that infection with *Schistosoma mansoni* may lead to secondary amyloidosis. In none of the four cases was there clinical evidence of another condition which may have caused the amyloidosis. In the third case a careful search at necropsy failed to show any other disease that could have led to amyloidosis. Also the clinical cure and the almost complete regression of renal and hepatic amyloid deposits in the first patient six months after antibilharzial treatment and the arrest of impairment of renal function in the second case one year after treatment lend further support to the idea that schistosomiasis caused the amyloidosis.

Since the first case, when amyloidosis was suspected clinically, we have routinely used a specific stain for amyloid on all biopsy material from patients with schistosomiasis and renal disease. This led to the discovery of the other three cases in the course of a year. Because of this unexpected finding we reviewed the published works but could find only one case of an association between bilharzia and amyloidosis.[6] This occurred in a 50-year-old woman with the nephrotic syndrome who was found at necropsy to have secondary amyloidosis. The authors postulated that this relation could have occurred through the hypergammaglobulinaemia that usually occurs in schistosomiasis. Recently Triger and Joekes[7] pointed to the ease with which amyloidosis may be missed unless specifically looked for and cited an example of a patient diagnosed on biopsy as having membraneous glomerulonephritis; at necropsy three years later he was found to have amyloidosis, and a review of the initial biopsy specimen with stains for amyloid showed that this had been the original condition. Workers in South America[4 5] studying the nephrotic syndrome and schistosomiasis have reported some cases of membraneous glomerulonephritis, but they do not say whether amyloid was specifically looked for. Our experience suggests that some of these might have been cases of amyloidosis.

In secondary amyloidosis renal involvement is considered to carry a poor prognosis, death resulting from progressive renal failure.[8 9] Nevertheless, Lowenstein and Gallo[10] described two patients with the nephrotic syndrome due to secondary amyloidosis in whom adequate treatment of the underlying cause resulted in clinical remission of the nephrotic syndrome and complete regression of the hepatic amyloid deposits, though renal deposits persisted. Triger and Joekes[7] reported five patients in whom clinical remission of the nephrotic syndrome was accompanied by regression of renal amyloid deposits after treatment of the primary cause. Our first patient showed a similar regression and, like these patients, he had adequate renal function before treatment. The second patient, with renal failure before treatment, still had heavy renal amyloid deposits one year after adequate treatment and cure of his schistosomiasis. Hence possibly early treatment before renal function is impaired may result in regression of renal amyloid deposits.

Glenner *et al*[11] have recently summarised the physicochemical and immunochemical evidence that indicates the immunoglobulin origin of the amyloid fibril protein. Work by Glenner *et al*[12] also suggested the existence of circulating immunoglobulin precursors of the amyloid fibril protein. One such possible immunoglobulin precursor is an antigen-antibody complex catabolised by macrophages[13]; the immunoglobulin is degraded in a manner that leads to fibril formation and deposition in organs such as liver and spleen. Recently Madawar and Voller[14] have shown circulating soluble antigens and antibodies in schistosomiasis, and these may possibly be the precursors of the amyloid deposits in schistosomiasis.

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